What if a placebo effect explained all the activity of depression treatments?

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such as escitalopram and desvenlafaxine. Moreover, fewer patients are then needed to identify antidepressant effect in controlled trials, which has important ethical implications (fewer patients need to receive placebo).

In my opinion, we need to aim at establishing "dose-remission" rather than dose-response relationship in future trials of antidepressants. The HAM-D-6 contains the core symptoms of depression by which to define the event of remission.

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What if a placebo effect explained all the activity of depression treatments?

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Many randomized trials have shown that when depressed patients receive no active treatment, e.g. they are administered pill placebo, a large part of them improve anyway. This improvement can be partly explained by natural remission or by the patients' expectations that a treatment will have an effect on their problems (even when they receive pill placebo). The corollary is that many patients remit even when undergoing exotic therapies, such as Argentian tango, swimming with dolphins or horticulture (1-3).

This phenomenon makes it difficult to examine the additional effects of specific treatments. This is not only true for pharmacotherapy, but also for psychotherapies for depression. In a recent meta-analysis, we found that 62% of patients meeting criteria for major depression at baseline did no longer meet these criteria after treatment (4). But among the patients receiving only care-as-usual, 48% also no longer met criteria for major depressive disorder. So, therapists may think that more than 60% of patients get better because of the psychotherapy, while in fact the additional benefit of psychotherapy over usual care is only 14%. Khan and Brown (5) indicate that comparable outcomes take place for pharmacotherapy, with symptom reduction of about 40% with antidepressants and 30% with placebo. That is in line with Kline's conclusion in 1964 that "in the treatment of depression, one always has an ally in the fact that most depressions terminate in spontaneous remissions" (6).

Given this large proportion of patients who remit spontaneously, patients as well as therapists can easily be led into the idea that their treatment is highly successful, while in fact the effects of this treatment may be only moderate. This may also explain why the exotic treatments mentioned earlier are believed by some to be effective, while most clinicians would consider the specific effects of such treatments as not very credible. "But we see that patients get better" is a phrase that supporters of such therapies often use.

Due to the discrepancy between the relatively high rate of spontaneous remission and the low additional value of specific (pharmacological and psychological) treatments, several important issues arise. One question is whether these treatments do in fact have any effects. Of course, randomized trials show that pharmacotherapy and psychotherapy are effective for treating depression, with small effect sizes of 0.30 for antidepressants (5) and 0.25 for psychotherapies (7). But we also know that these effects are much higher when risk of bias is not taken into account. In fact, only the highest quality studies show such small effects, and only after publication bias has been adjusted for.

But suppose there is still a bias lingering in these trials. For example, since patients getting a placebo know that they are not receiving active medication because they experience no side effects, this breaks the blinding and serves to lower their expectations.

A meta-analysis of trials with active placebos pointed exactly in this direction (8). Or investigators' choices may influence the trial outcomes in ways that are just not known, for example by selecting those patients who are expected to respond well to treatment but not to placebo (9). The effects of the active treatments are so small that only slight tweaking because of some bias may further them, and make them clinically irrelevant. The same is true for psychotherapies. Their effects compared with pill placebo are very small and, because patients cannot be blinded at all, expectations may have a considerable effect on the outcomes. Only a small adjustment because of an unknown risk of bias could move these effects into clinical irrelevance as well.

The other implication is that research should focus much more on how spontaneous remission takes place. Now most of the research is focused on the brain changes and the psychological mechanisms involved in the action of biological and psychological therapies. However, the process through which spontaneous remission occurs is at least as important as the mechanisms through which these specific treatments work, particularly since their additional effectiveness is not as high as has been thought for a long time.

Hence, a clinical issue in need of much more investigation is by what mechanisms spontaneous remission can be optimized. For example, it can be assumed that when expectations of outcome are higher, spontaneous remission is more likely to occur. If we understood this process better, we could also find ways to optimize expectations and thus increase remission rates. That would eventually reduce the relative contribution of current treatments towards remission, though they still may lead to better outcomes for patients.

Khan and Brown conclude that the effects of antidepressants are modest, and other research shows that the same holds for psychological treatments for depression. We argue that the high rate of spontaneous remission introduces considerable confusion about the effectiveness of treatments. In order to improve outcomes for patients we have to face facts, and focus much more on the process of natural recovery instead of on the limited contributions of specific treatments.

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